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EXAMINER	
ROMEO, DAVID S	

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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Application Number: 09/800,541
Filing Date: March 07, 2001
Appellant(s): KNUDSEN, LISELOTTE BJERRE

Richard W. Bork
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed January 3, 2005.

JHC

(1) Real Party in Interest

A statement identifying the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

A statement identifying the related appeals and interferences which will directly affect or be directly affected by or have a bearing on the decision in the pending appeal is contained in the brief.

(3) Status of Claims

The statement of the status of the claims contained in the brief is incorrect. A correct statement of the status of the claims is as follows:

This appeal involves claims 26-29 and 36-72.

The elected species Arg^{34},Lys^{26}(N^{M}-K-Glu(N^{I}-hexadecanoyl)))GLP-1(7-37) and the species GLP-1 (7-36)amide, exendin-3, and exendin-4 are being examined.

Claims 26-29 and 36-72 are withdrawn from consideration to the extent that they are not directed to the species Arg^{34},Lys^{26}(N^{M}-K-Glu(N^{I}-hexadecanoyl)))GLP-1(7-37), GLP-1 (7-36)amide, exendin-3, and exendin-4.

(4) Status of Amendments After Final

The appellant's statement of the status of amendments after final rejection contained in the brief is correct.

(5) Summary of Invention

The summary of invention contained in the brief is correct.

(6) Issues

The appellant's statement of the issues in the brief is substantially correct.

The rejection of claims 45, 49, 55, 59, 65, 69 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention because it is unclear if the analog is GLP-1(7-37) with a single amino acid substitution or some wholly undefined compound comprising an amino acid that is different from an amino acid in the corresponding position of GLP-1(7-37) is withdrawn.

(7) Grouping of Claims

The rejection of claims 26-29 and 36-72 stand or fall together because appellant's brief does not include a statement that this grouping of claims does not stand or fall together and reasons in support thereof. See 37 CFR 1.192(c)(7).

(8) Claims Appealed

The copy of the appealed claims contained in the Appendix to the brief is correct.

(9) Prior Art of Record

5,424,286	ENG	06-1995
5,631,224	EFENDIC ET AL.	05-1997
6,268,343	KNUDSEN ET AL.	07-2001
6,458,924	KNUDSEN ET AL.	10-2002

Raufman et al. Truncated glucagon-like peptide-1 interacts with exendin receptors on dispersed acini from guinea pig pancreas. Identification of a mammalian analogue of the reptilian peptide exendin-4. J Biol Chem. 1992 Oct 25;267(30):21432-7.

Howard BV. Lipoprotein metabolism in diabetes. Curr Opin Lipidol. 1994 Jun;5(3):216-20.

Juntti-Berggren et al. The antidiabetogenic effect of GLP-1 is maintained during a 7-day treatment period and improves diabetic dyslipoproteinemia in NIDDM patients. Diabetes Care. 1996 Nov;19(11):1200-6.

(10a) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

Claims 26-29, 36-42, 44-46, 48, 49, 51, 52, 54-56, 58, 59, 61, 62, 64-66, 68, 69, 71, 72 are rejected under 35 U.S.C. 102(b) as being anticipated by Eng (U. S. Patent No. 5,424,286) as evidenced by Raufman (J Biol Chem. 1992 Oct 25;267(30):21432-7) and Howard (Curr Opin Lipidol. 1994 Jun;5(3):216-20).

Eng discloses pharmaceutical compositions containing exendin-3 or exendin-4, or any combination thereof, and methods for the treatment of diabetes mellitus and the prevention of hyperglycemia (column 2, lines 35-40). Exendin-3 and exendin-4 are analogs or derivatives or derivatives of an analogue of GLP-1(7-37) or exendin-4, in the absence of evidence to the contrary.

Patients with diabetes mellitus overlap "a patient in need of having one or more serum lipid levels lowered," "a patient in need of reduction of said LDL:HDL ratio," and "a patient in need of reduction of the serum level of lipoprotein A (lp(A)) and/or apolipoprotein A (apo(A))" because:

Firstly, the present specification discloses that lowering levels of plasma lipids and lipoproteins lowers the risk of cardiovascular disease (specification, page 2, full paragraph 2).

Therefore, essentially any and/or all patients, including diabetic and/or obese patients, including such patients with or without cardiovascular disease, are in need of such treatment because such treatment lowers the risk of cardiovascular disease, in accordance with the present specification at page 2, full paragraph 2.

Furthermore, objects of the present invention are to provide:

> compositions which can effectively be used in the treatment or prophylaxis of dyslipidaemia, hyperlipoproteinaemia, hypertriglyceridaemia, hyperlipidaemia or hypercholesterolaemia (specification, page 2, full paragraph 4);
>
> methods for treating a human having a disease-state which is alleviated by lowering total one or more serum lipids (pages 3-4, and 6);
>
> a GLP-1 agonist for the manufacture of a medicament for treating dyslipidemia in a diabetic patient (page 7; full paragraph 2);
>
> a GLP-1 agonist for the manufacture of a medicament for treating dyslipidemia in a patient having type 2 diabetes, also known as NIDDM (page 7, full paragraph 8);
>
> treatment for diseases that may be alleviated by lowering serum lipid levels, including, e.g., cardiovascular disease and diabetes (Abstract).

The claimed invention is exemplified in a rat model of Type 2 diabetes (Example 2, pages 43-44). Thus, the present specification contemplates the treatment of diabetes and the treatment of diabetes is consistent with the present specification. The examiner uses the present specification as a definition of the term "patient in need of" the claimed treatments.

Secondly, Howard teaches that:

> dyslipidemia contributes to the atherosclerotic process in diabetic individual (paragraph at top of page 216);
>
> the leading cause of death for individuals with diabetes is cardiovascular disease, and one of the most important factors that contribute to this is the alteration in lipoproteins that occur in diabetic subjects (page 216, left column, "Introduction");

> Agents which improve glycemic control sometimes also result in improvements in diabetic dyslipidemia (page 218, right column, full paragraph 1).
>
> the cornerstone of therapy for diabetic patients should essentially consider the management of dyslipidemia along with the hyperglycemia, hypertension, and obesity (page 219, left column).

The examiner uses Howard to show that a diabetic patient is a "patient in need of" the claimed treatments because the treatment of diabetes overlaps the treatment of dyslipidemia, cardiovascular disease, hypertension, and obesity, and that Eng would administer exendin-3 or exendin-4 to a diabetic patient with the intention of improving glycemic control and improving diabetic dyslipidemia because the cornerstone of therapy for diabetic patients should essentially consider the management of dyslipidemia along with the hyperglycemia, hypertension, and obesity and agents which improve glycemic control sometimes also result in improvements in diabetic dyslipidemia.

The examiner uses Raufman to show that GLP-1(7-36) interacts with exendin receptors. See Raufman, page 21432, right column, last full paragraph. Accordingly, an exendin receptor is a GLP-1 receptor. Exendin-3 or -4 binds a GLP-1 receptor, which in this case happens to be an exendin receptor, with an affinity constant below 1 μM, in the absence of evidence to the contrary.

Burden is shifted to applicant to distinguish Applicant's invention from Eng's invention.

(10b) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

Claims 26, 27, 29, 36, 37, 39, 40, 42-46, 48, 49, 52-56, 58, 59, 62-66, 68, 69, 72 are rejected under 35 U.S.C. 102(b) as being anticipated by Efendic (U. S. Patent No. 5,631,224) as evidenced by Howard (Curr Opin Lipidol. 1994 Jun;5(3):216-20).

Efendic discloses infusing GLP-1 (7-36)amide at a rate of 0.75 pmol per kilogram of body weight per minute in insulin treated obese NIDDM patients (paragraph bridging columns 5-6). It is reasonable to assume that GLP-1 (7-36)amide binds a GLP-1 receptor with an affinity constant below 1 μM, in the absence of evidence to the contrary. GLP-1 (7-36)amide is an analog or derivative or a derivative of an analogue of GLP-1(7-37) or exendin-4, in the absence of evidence to the contrary.

Obese NIDDM patients overlap "a patient in need of having one or more serum lipid levels lowered," "a patient in need of reduction of said LDL:HDL ratio," and "a patient in need of reduction of the serum level of lipoprotein A (lp(A)) and/or apolipoprotein (apo(A))" because:

Firstly, the present specification discloses that lowering levels of plasma lipids and lipoproteins lowers the risk of cardiovascular disease (specification, page 2, full paragraph 2). Therefore, essentially any and/or all patients, including diabetic and/or obese patients, including such patients with or without cardiovascular disease, are in need of such treatment because such treatment lowers the risk of cardiovascular disease, in accordance with the present specification at page 2, full paragraph 2.

Furthermore, objects of the present invention are to provide:

compositions which can effectively be used in the treatment or prophylaxis of dyslipidaemia, hyperlipoproteinaemia, hypertriglyceridaemia, hyperlipidaemia or hypercholesterolaemia (specification, page 2, full paragraph 4);

methods for treating a human having a disease-state which is alleviated by lowering total one or more serum lipids (pages 3-4, and 6);

a GLP-1 agonist for the manufacture of a medicament for treating dyslipidemia in a diabetic patient (page 7, full paragraph 2);

a GLP-1 agonist for the manufacture of a medicament for treating dyslipidemia in a patient having type 2 diabetes, also known as NIDDM (page 7, full paragraph 8);

treatment for diseases that may be alleviated by lowering serum lipid levels, including, e.g., cardiovascular disease and diabetes (Abstract).

The claimed invention is exemplified in a rat model of Type 2 diabetes (Example 2, pages 43-44). Thus, the present specification contemplates the treatment of diabetes and the treatment of diabetes is consistent with the present specification. The examiner uses the present specification as a definition of the term "patient in need of" the claimed treatments.

Secondly, Howard teaches that:

dyslipidemia contributes to the atherosclerotic process in diabetic individuals (paragraph at top of page 216);

the leading cause of death for individuals with diabetes is cardiovascular disease, and one of the most important factors that contribute to this is the alteration in lipoproteins that occur in diabetic subjects (page 216, left column, "Introduction");

Agents which improve glycemic control sometimes also result in improvements in diabetic dyslipidemia (page 218, right column, full paragraph 1).

the cornerstone of therapy for diabetic patients should essentially consider the management of dyslipidemia along with the hyperglycemia, hypertension, and obesity (page 219, left column).

The examiner uses Howard to show that an obese, diabetic patient is a "patient in need of" the claimed treatments because the treatment of diabetes overlaps the treatment of

dyslipidemia, cardiovascular disease, hypertension, and obesity, and that Efendic would administer GLP-1 (7-36)amide to a diabetic patient with the intention of improving glycemic control and improving diabetic dyslipidemia because the cornerstone of therapy for diabetic patients should essentially consider the management of dyslipidemia along with the hyperglycemia, hypertension, and obesity and agents which improve glycemic control sometimes also result in improvements in diabetic dyslipidemia.

Burden is shifted to applicant to distinguish Applicant's invention from Efendic.

(11a-b)Response to Argument

Appellants argue that Eng only discloses the use of exendin-3 and exendin-4 with the intent of treating diabetes mellitus and preventing hyperglycemia. Eng does not administer exendin-3 or -4 with the intention of lowering the levels of one or more serum lipids, reducing the serum LDL:HDL ratio, or reducing the serum level of lipoprotein A and/or apolipoprotein A in a patient in need of each.

Appellants argue that it is questionable whether one would assume that exendin-3 and -4 would be useful for blood lipid control because of the activity profile of exendins and because Eng does not correlate the treatment of diabetes mellitus or hyperglycemia with lowering the levels of one or more serum lipids, reducing the serum LDL:HDL ratio, or reducing the serum level of lipoprotein A and/or apolipoprotein A in a patient in need of each. Appellants' arguments have been fully considered but they are not persuasive.

Appellants have not presented any experimental data showing that the activity profile of exendins is not correlated with achieving the results in the present claims. The examiner concludes that appellants' argument is mere argument. Arguments of counsel cannot take the

place of evidence in the record. Furthermore, the examiner uses Howard to show that a diabetic patient is a "patient in need of" the claimed treatments because the treatment of diabetes overlaps the treatment of dyslipidemia, cardiovascular disease, hypertension, and obesity, and that Eng would administer exendin-3 or exendin-4 to a diabetic patient with the intention of improving glycemic control and improving diabetic dyslipidemia because the cornerstone of therapy for diabetic patients should essentially consider the management of dyslipidemia along with the hyperglycemia, hypertension, and obesity and agents which improve glycemic control sometimes also result in improvements in diabetic dyslipidemia.

Appellants argue that Raufman and Howard do nothing to cure the deficiencies in Eng because there is no disclosure in the prior art of using GLP-1(7-36) or an exendin with the intent of achieving the results in the present claims. Appellants' arguments have been fully considered but they are not persuasive.

The examiner has cited Raufman to show that GLP-1(7-36) interacts with exendin receptors. Therefore, an exendin receptor is a GLP-1 receptor. Therefore, exendin-3 or -4 binds a GLP-1 receptor, which in this case happens to be an exendin receptor, with an affinity constant below 1 μM, in the absence of evidence to the contrary, as required by claims 29, 39, and 42.

The examiner has cited Howard to show that a diabetic patient is a "patient in need of" the claimed treatments because the treatment of diabetes overlaps the treatment of dyslipidemia, cardiovascular disease, hypertension, and obesity, and that Eng would administer exendin-3 or exendin-4 to a diabetic patient with the intention of improving glycemic control and improving diabetic dyslipidemia because the cornerstone of therapy for diabetic patients should essentially consider the management of dyslipidemia along with the hyperglycemia, hypertension, and

obesity and agents which improve glycemic control sometimes also result in improvements in diabetic dyslipidemia.

Appellants argue that the pending claims do not call for the treatment of cardiovascular diseases. Appellants' arguments have been fully considered but they are not persuasive.

The pending claims are directed to or encompass the treatment of "a patient in need of having one or more serum lipid levels lowered," "a patient in need of reduction of said LDL:HDL ratio," and "a patient in need of reduction of the serum level of lipoprotein A (lp(A)) and/or apolipoprotein A (apo(A))." The present specification discloses:

> Treatment for diseases that may be alleviated by lowering serum lipid levels, including, e.g., cardiovascular disease and diabetes (Abstract).
>
> If one concurs with the notion that atherosclerosis and associated cardiovascular diseases are related to abnormal levels of plasma lipids and lipoproteins, then lowering them represent a desirable therapeutic goal. Page 2, full paragraph 2.
>
> One object of the present invention is to provide compositions which can effectively be used in the treatment or prophylaxis of dyslipidaemia, hyperlipoproteinaemia, hypertriglyceridaemia, hyperlipidaemia or hypercholesterolaemia. Page 2, full paragraph 4.
>
> In a further aspect the invention relates to a method of treating a disease selected from cerebrovascular diseases, stroke, cerebral hemorrhage, coronary heart disease, coronary artery disease, diabetic vasculopathy, atherosclerosis, peripheral atherosclerosis, arteriosclerosis, ischemic heart disease, stable and unstable angina pectoris, cardiac insufficiency, myocardial infarction, restenosis, peripheral artery disease, intermittent claudication, aneurisms of aorta and other large arteries, or bypass graft stenosis, which method comprises administering to a subject an effective amount of a GLP-1 agonist. Each of these diseases is considered an individual embodiment of the invention. Page 6, full paragraph 6.
>
> In a further aspect the invention relates to a method of treating cardiovascular diseases which method comprises administering to a subject an effective amount of a GLP-1 agonist. Page 6, last full paragraph.

Using the present specification as a definition of the term "patient in need of" the claimed treatments, the examiner concludes that the claimed treatments of a "patient in need of" the claimed treatments overlaps the treatment of cardiovascular disease.

Appellants argue that Howard's disclosure does not show that Eng discloses administering exendin-3 and -4 with the intent of achieving the results in the present claims. Appellants' arguments have been fully considered but they are not persuasive. Howard shows that a diabetic patient is a "patient in need of" the claimed treatments because the treatment of diabetes overlaps the treatment of dyslipidemia, cardiovascular disease, hypertension, and obesity. Howard also shows that Eng would administer exendin-3 or exendin-4 to a diabetic patient with the intention of improving glycemic control and improving diabetic dyslipidemia, i.e., with the intent of achieving the results in the present claims, because the cornerstone of therapy for diabetic patients should essentially consider the management of dyslipidemia along with the hyperglycemia, hypertension, and obesity and agents which improve glycemic control sometimes also result in improvements in diabetic dyslipidemia.

Appellants argue that Efendic does not administer GLP-1 (7-36)amide with the intention of achieving the results in the present claims and that Howard does not make Efendic an anticipating reference, just as it did not make Eng an anticipating reference, expressly or inherently. Appellants' arguments have been fully considered but they are not persuasive.

The examiner uses Howard to show that an obese, diabetic patient is a "patient in need of" the claimed treatments because the treatment of diabetes overlaps the treatment of dyslipidemia, cardiovascular disease, hypertension, and obesity, and that Efendic would administer GLP-1 (7-36)amide to a diabetic patient with the intention of improving glycemic

control and improving diabetic dyslipidemia because the cornerstone of therapy for diabetic patients should essentially consider the management of dyslipidemia along with the hyperglycemia, hypertension, and obesity and agents which improve glycemic control sometimes also result in improvements in diabetic dyslipidemia.

Appellants argue that just as in Rapoport, the prior art relied upon by the examiner cannot anticipate any of the claims because the prior art does not disclose administering something to patients with the specific intent of achieving the results in the present claims. Applicant's arguments have been fully considered but they are not persuasive. In Rapoport, both intrinsic evidence and the plain meaning of the term "method for treatment of sleep apneas" supported construction of the term as being limited to treatment of the underlying sleep apnea disorder itself, and not encompassing treatment of anxiety and other secondary symptoms related to sleep apnea. However, the present specification discloses treatment for diseases that may be alleviated by lowering serum lipid levels, including, e.g., cardiovascular disease and diabetes, by administering a GLP-1 agonist. Thus, a "patient in need of" the claimed treatments overlaps the treatment of cardiovascular disease and diabetes, as discussed above. Eng and Efendic disclose the treatment of diabetes with an exendin and GLP-1(7-36)amide, respectively. The present claims are directed to or encompass the administration of exendin-3, exendin-4 and GLP-1(7-36)amide. Furthermore, Howard shows that Eng or Efendic would administer a GLP-1 agonist to a diabetic patient with the intention of improving glycemic control and improving diabetic dyslipidemia because the cornerstone of therapy for diabetic patients should essentially consider the management of dyslipidemia along with the hyperglycemia, hypertension, and obesity and agents which improve glycemic control sometimes also result in improvements in diabetic

dyslipidemia. In other words, Eng and Efendic encompass achieving the results in the present claims.

(10c) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

Claims 26-29, 36-72 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of lowering plasma levels of triglycerides, free fatty acids, or total cholesterol, does not reasonably provide enablement for a method of lowering one or more serum lipids, of reducing the serum LDL:HDL ratio, or of reducing the serum level of lp(A) or apo(A).

The specification envisions lowering one or more serum lipids, reducing the serum LDL:HDL ratio, and reducing the serum level of lp(A) or apo(A). The only working examples in the specification show lowering plasma levels of triglycerides, free fatty acids, or total cholesterol. The claims are directed to or encompass lowering one or more serum lipids, reducing the serum LDL:HDL ratio, and reducing the serum level of lp(A) or apo(A). However, no changes were observed in the levels of LDL and HDL cholesterol after administration of GLP-1. See Juntti-Berggren (Diabetes Care. 1996 Nov;19(11):1200-6), page 1200, "RESULTS". This is objective evidence that the full scope of the claims is not enabled. No guidance for, or working examples of, practicing the invention commensurate with the full scope of the claims is provided. The skilled artisan is left to unduly extensive experimentation involving random, trial and error, and fundamentally unpredictable experimentation.

(11c) Response to Argument

Appellants argue that Juntti-Berggren is not relevant because: firstly, Juntti-Berggren is only a single protocol, no information is given about the patients' medical history, physical condition, activity, or regular diet, and there was no optimization of doses; and secondly, the standard deviations in Table 4 make the data suspect. Appellants' reference to page 43, lines 1-7 of the present specification are noted. Appellants further argue that Juntti-Berggren does not given any reason to doubt the objective truth of statements in the present application. Appellants' arguments have been fully considered but they are not persuasive.

Juntti-Berggren discloses that GLP-1 improves diabetic dyslipoproteinemia in NIDDM patients (page 1200, Title). The present specification discloses a GLP-1 agonist for the manufacture of a medicament for treating dyslipidemia in a patient having type 2 diabetes, also known as NIDDM (page 7, full paragraph 8), a treatment for diseases that may be alleviated by lowering serum lipid levels, including, e.g., cardiovascular disease and diabetes (Abstract), and the use of a GLP-1 agonist for the manufacture of a medicament for treating dyslipidemia in a patient having type 2 diabetes, in a regimen which additionally comprises treatment with insulin (page 8, full paragraph 6). Insofar as the treatment of dyslipidemia or routine optimization of doses with a GLP-1 agonist is concerned, there is nothing in Juntti-Berggren that is inconsistent with the present specification. Therefore, Juntti-Berggren is relevant. However, Juntti-Berggren did not observe any changes in the levels of LDL and HDL cholesterol after administration of GLP-1, thereby making the full scope of the presently claimed invention suspect. Appellants have not presented any experimental data showing that a single protocol, the patients' medical history, physical condition, activity, or regular diet, is correlated with the observed lack of

changes in the levels of LDL and HDL cholesterol after administration of GLP-1. The examiner concludes that appellants' argument is mere argument. Arguments of counsel cannot take the place of evidence in the record.

The data in Juntti-Berggren's Table 4 (page 1204) is clear and unambiguous — no changes were observed in the levels of LDL and HDL cholesterol. Appellants have not presented any evidence or reasoning that would lead one to suspect the data Table 4 (page 1204). The examiner concludes that appellants' argument is mere argument. Arguments of counsel cannot take the place of evidence in the record.

(10d) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

Claims 26-29, 36-72 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The specification envisions lowering one or more serum lipids, reducing the serum LDL:HDL ratio, and reducing the serum level of lp(A) or apo(A). The only working examples in the specification show lowering plasma levels of triglycerides, free fatty acids, or total cholesterol. The claims are directed to or encompass lowering one or more serum lipids, reducing the serum LDL:HDL ratio, and reducing the serum level of lp(A) or apo(A). However, no changes were observed in the levels of LDL and HDL cholesterol after administration of GLP-1. See Juntti-Berggren (Diabetes Care. 1996 Nov;19(11):1200-6), page 1200,

"RESULTS". This is objective evidence that the full scope of the claims is not described. No specific guidance for, or working examples of, practicing the invention commensurate with the full scope of the claims is described.

(11d) Response to Argument

Appellants argue that Juntti-Berggren is not relevant because: firstly, Juntti-Berggren is only a single protocol, no information is given about the patients' medical history, physical condition, activity, or regular diet, and there was no optimization of doses; and secondly, the standard deviations in Table 4 make the data suspect. Appellants' reference to page 43, lines 1-7 of the present specification are noted. Appellants argue that Juntti-Berggren does not given any reason to doubt the objective truth of statements in the present application. Appellants argue that there is *ipsis verbis* support in the present specification for the pending claims. Appellants' arguments have been fully considered but they are not persuasive.

Juntti-Berggren discloses that GLP-1 improves diabetic dyslipoproteinemia in NIDDM patients (page 1200, Title). The present specification discloses a GLP-1 agonist for the manufacture of a medicament for treating dyslipidemia in a patient having type 2 diabetes, also known as NIDDM (page 7, full paragraph 8), a treatment for diseases that may be alleviated by lowering serum lipid levels, including, e.g., cardiovascular disease and diabetes (Abstract), and the use of a GLP-1 agonist for the manufacture of a medicament for treating dyslipidemia in a patient having type 2 diabetes, in a regimen which additionally comprises treatment with insulin (page 8, full paragraph 6). Insofar as the treatment of dyslipidemia or routine optimization of doses with a GLP-1 agonist is concerned, there is nothing in Juntti-Berggren that is inconsistent with the present specification. Therefore, Juntti-Berggren is relevant. The present claims are

directed to or encompass lowering one or more serum lipid levels, including LDL; small, dense LDL; VLDL; triglycerides; free fatty acids; cholesterol; and HDL, reducing the LDL:HDL ratio, and reducing the serum level of lipoprotein A and/or apolipoprotein A. The only working examples in the specification show lowering plasma levels of triglycerides, free fatty acids, or total cholesterol. However, Juntti-Berggren did not observe any changes in the levels of LDL and HDL cholesterol after administration of GLP-1. The examiner concludes that the species exemplified and the *ipsis verbis* support in the present specification are inadequate to determine that appellants were in possession of the full scope of the claimed invention. Appellants have not presented any experimental data showing that a single protocol, the patients' medical history, physical condition, activity, or regular diet, is correlated with the observed lack of changes in the levels of LDL and HDL cholesterol after administration of GLP-1. The examiner concludes that appellants' argument is mere argument. Arguments of counsel cannot take the place of evidence in the record.

The data in Juntti-Berggren's Table 4 (page 1204) is clear and unambiguous — no changes were observed in the levels of LDL and HDL cholesterol. Appellants have not presented any evidence or reasoning that would lead one to suspect the data Table 4 (page 1204). The examiner concludes that appellants' argument is mere argument. Arguments of counsel cannot take the place of evidence in the record.

(10e) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

Claims 26, 27, 29, 36, 37, 39, 40, 42, 44-49, 52, 54-59, 62, 64-69, 72 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the

specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are directed to or encompass a genus of compounds that are GLP-1 agonists, wherein the agonist is an "analogue," "derivative," or "derivative of an analogue" of the specific GLP-1 agonists recited in the present claims. The specification and claim do not indicate what distinguishing attributes shared by the members of the genus. The specification and claim do not place any structural limitations on the structure of the agonist. Thus, the scope of the claim includes numerous structural variants, and the genus is highly variant because there are no structural limitations to the genus. Structural features that could distinguish compounds in the genus from others in the protein class are missing from the disclosure. No common structural attributes identify the members of the genus. The general knowledge and level of skill in the art do not supplement the omitted description because specific, not general, guidance is what is needed. Although it might be obvious for the skilled artisan to screen for compounds with GLP-1 agonist activity, the written description requirement is not satisfied by that which is obvious over what is disclosed; it is satisfied by that which is disclosed. Since the disclosure fails to describe the common attributes or characteristics that identify members of the genus, and because the genus is highly variant, the specific structural analogs of GLP-1 disclosed in the preset specification, alone are insufficient to describe the genus. One of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus. Thus, applicant was not in possession of the claimed genus.

(11e) Response to Argument

Appellants argue that the present specification provides numerous examples of such compounds, that these terms are well known in the art, and that these terms have been accepted by the U.S.P.T.O. in other patents. Appellants' arguments have been fully considered but they are not persuasive.

The present specification discloses:

> the GLP-1 agonist is a GLP-1 analogue (page 12, line 15);
>
> GLP-1 analogues include, but are not limited to the specific, exemplified GLP-1 analogues (paragraph bridging pages 17-18);
>
> the GLP-1 agonist is a GLP-1 derivative (page 18, line 23);
>
> GLP-1 derivatives include, but are not limited to the specific, exemplified GLP-1 derivatives (paragraph bridging pages 27-39);
>
> the GLP-1 agonist is a non-peptide (page 40, line 16);
>
> a GLP-1 agonist is also intended to comprise active metabolites and prodrugs thereof, such as active metabolites and prodrugs of GLP-1 or an analogue or a derivative thereof, or exendin or an analogue or a derivative thereof, or a non-peptide (paragraph bridging pages 40-41);
>
> the designation "an analogue" is used to designate a peptide wherein one or more amino acid residues of the parent peptide have been substituted by another amino acid residue and/or wherein one or more amino acid residues of the parent peptide have been deleted and/or wherein one or more amino acid residues have been added to the parent peptide. Such addition can take place either in the peptide, at the N-terminal end or at the C-terminal end of the parent peptide, or any combination thereof. Page 41, full paragraph 1.
>
> The term "derivative" is used in the present text to designate a peptide in which one or more of the amino acid residues of the parent peptide have been chemically modified, e.g. by alkylation, acylation, ester formation or amide formation (page 41, full paragraph 2);
>
> The term "a GLP-1 derivative" is used in the present text to designate a derivative of GLP-1 or an analogue thereof (page 41, full paragraph 3).

It is apparent that there is no correlation between the structure of the "analogue," "derivative," or "derivative of an analogue" recited in the present claims and the specific examples of a GLP-1 agonist or derivative disclosed in the present specification because there is no structure associated with the "analogue," "derivative," or "derivative of an analogue" recited in the present claims. Therefore, Appellants' reliance on the specific examples of such compounds to describe the genus is inadequate. Suffice it to say that each case must be decided on its own merits based on the evidence of record.

(10f) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

Claims 44-49, 52, 54-59, 62, 64-69, 72 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claims 44-49, 52, 54-59, 62, 64-69, 72 are indefinite because they recite the term "analogue" or "derivative," "derivative of an analogue," or "exendin-4 analogue." Because the instant specification does not identify that material element or combination of elements which is unique to, and, therefore, definitive of "analogue" or "derivative," "derivative of an analogue," or "exendin-4 analogue" an artisan cannot determine what additional or material limitations are placed upon a claim by the presence of this element. The metes and bounds are not clearly set forth.

(11f) Response to Argument

Appellants argue that the present specification provides numerous examples of such compounds, that these terms are well known in the art, and that these terms have been accepted

by the U.S.P.T.O. in other patents. Appellants' arguments have been fully considered but they are not persuasive.

The present specification discloses:

the GLP-1 agonist is a GLP-1 analogue (page 12, line 15);

GLP-1 analogues include, but are not limited to the specific, exemplified GLP-1 analogues (paragraph bridging pages 17-18);

the GLP-1 agonist is a GLP-1 derivative (page 18, line 23);

GLP-1 derivatives include, but are not limited to the specific, exemplified GLP-1 derivatives (paragraph bridging pages 27-39);

the GLP-1 agonist is a non-peptide (page 40, line 16);

a GLP-1 agonist is also intended to comprise active metabolites and prodrugs thereof, such as active metabolites and prodrugs of GLP-1 or an analogue or a derivative thereof, or exendin or an analogue or a derivative thereof, or a non-peptide (paragraph bridging pages 40-41);

the designation "an analogue" is used to designate a peptide wherein one or more amino acid residues of the parent peptide have been substituted by another amino acid residue and/or wherein one or more amino acid residues of the parent peptide have been deleted and/or wherein one or more amino acid residues have been added to the parent peptide. Such addition can take place either in the peptide, at the N-terminal end or at the C-terminal end of the parent peptide, or any combination thereof. Page 41, full paragraph 1.

The term "derivative" is used in the present text to designate a peptide in which one or more of the amino acid residues of the parent peptide have been chemically modified, e.g. by alkylation, acylation, ester formation or amide formation (page 41, full paragraph 2);

The term "a GLP-1 derivative" is used in the present text to designate a derivative of GLP-1 or an analogue thereof (page 41, full paragraph 3).

It is apparent that there is no correlation between the structure of the "analogue," "derivative," or "derivative of an analogue" recited in the present claims and the specific

examples of a GLP-1 agonist or derivative disclosed in the present specification because there is no structure associated with the "analogue," "derivative," or "derivative of an analogue" recited in the present claims. Therefore, Appellants' reliance on the specific examples of such compounds to set forth the metes and bounds of an "analogue" or "derivative," "derivative of an analogue," or "exendin-4 analogue" are unpersuasive. Suffice it to say that each case must be decided on its own merits based on the evidence of record.

(10g) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

Claims 26-29, 36-42, 44-50, 52, 54-60, 62, 64-70, 72 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 39, 40 of U.S. Patent No. 6,268,343 in view of Howard (Diabetes Care. 1996 Nov;19(11):1200-6) and Efendic (U. S. Patent No. 5,631,224).

Although the conflicting claims are not identical, they are not patentably distinct from each other because each of set of claims is directed to or encompasses the administration of Arg^{34},Lys^{26}(N^{M}-K-Glu(N^{I}-hexadecanoyl)))GLP-1(7-37) for the treatment of diabetes or obesity.

Essentially any and/or all patients, including diabetic and/or obese patients, including such patients with or without cardiovascular disease, are in need of such treatment because such treatment lowers the risk of cardiovascular disease in accordance with the present specification at page 2, full paragraph 2. The examiner uses the present specification as a definition of the term "patient in need of such treatment". Howard teaches that the cornerstone of therapy for diabetic patients should essentially consider the management of dyslipidemia along with the hyperglycemia, hypertension, and obesity (page 219, left column). An understanding of

lipoprotein metabolism in diabetes is essential because dyslipidemia contributes to the atherosclerotic process in diabetic individual (page 216, Abstract). The leading cause of death for individuals with diabetes is cardiovascular disease, and one of the most important factors that contribute to this is the alteration in lipoproteins that occur in diabetic subjects (page 216, left column, "Introduction"). Diabetic patients can also be obese patients, as evidenced by Efendic (paragraph bridging columns 5-6).

(10h) Grounds of Rejection

Claims 26-29, 36-42, 44-50, 52, 54-60, 62, 64-70, 72 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 19, 20 of U. S. Patent No. 6,458,924 in view of Howard (Diabetes Care. 1996 Nov;19(11):1200-6) and Efendic (U. S. Patent No. 5,631,224).

Although the conflicting claims are not identical, they are not patentably distinct from each other because each of set of claims is directed to or encompasses the administration of Arg^{34},Lys^{26}(N^{M}-K-Glu(N^{I}-hexadecanoyl)))GLP-1(7-37) for the treatment of diabetes or obesity. Essentially any and/or all patients, including diabetic and/or obese patients, including such patients with or without cardiovascular disease, are in need of such treatment because such treatment lowers the risk of cardiovascular disease in accordance with the present specification at page 2, full paragraph 2. The examiner uses the present specification as a definition of the term "patient in need of such treatment". Howard teaches that the cornerstone of therapy for diabetic patients should essentially consider the management of dyslipidemia along with the hyperglycemia, hypertension, and obesity (page 219, left column). An understanding of lipoprotein metabolism in diabetes is essential because dyslipidemia contributes to the

atherosclerotic process in diabetic individual (page 216, Abstract). The leading cause of death for individuals with diabetes is cardiovascular disease, and one of the most important factors that contribute to this is the alteration in lipoproteins that occur in diabetic subjects (page 216, left column, "Introduction"). Diabetic patients can also be obese patients, as evidenced by Efendic (paragraph bridging columns 5-6).

(11g-h) Response to Argument

Appellants argue that every claim requires that the method be practiced with the intent to achieve the stated objective and that the claims of the cited patents do not expressly or inherently disclose the administration of a GLP-1 agonist with the intent of achieving the results in the present claims. Appellants argue that Howard and Efendic do nothing to cure this deficiency. Appellants argue that a patient's knowledge of his condition is not a disclosure of an intent to treat any such condition. Appellants' arguments have been fully considered but they are not persuasive.

Patients with diabetes mellitus and/or obesity overlap "a patient in need of having one or more serum lipid levels lowered," "a patient in need of reduction of said LDL:HDL ratio," and "a patient in need of reduction of the serum level of lipoprotein A (lp(A)) and/or apolipoprotein A (apo(A))" because:

Firstly, the present specification discloses that lowering levels of plasma lipids and lipoproteins lowers the risk of cardiovascular disease (specification, page 2, full paragraph 2). Therefore, essentially any and/or all patients, including diabetic and/or obese patients, including such patients with or without cardiovascular disease, are in need of such treatment because such

treatment lowers the risk of cardiovascular disease, in accordance with the present specification at page 2, full paragraph 2.

Furthermore, objects of the present invention are to provide:

> compositions which can effectively be used in the treatment or prophylaxis of dyslipidaemia, hyperlipoproteinaemia, hypertriglyceridaemia, hyperlipidaemia or hypercholesterolaemia (specification, page 2, full paragraph 4);
>
> methods for treating a human having a disease-state which is alleviated by lowering total one or more serum lipids (pages 3-4, and 6);
>
> a GLP-1 agonist for the manufacture of a medicament for treating dyslipidemia in a diabetic patient (page 7, full paragraph 2);
>
> a GLP-1 agonist for the manufacture of a medicament for treating dyslipidemia in a patient having type 2 diabetes, also known as NIDDM (page 7, full paragraph 8);
>
> treatment for diseases that may be alleviated by lowering serum lipid levels, including, e.g., cardiovascular disease and diabetes (Abstract).

Thus, the present specification contemplates the treatment of diabetes and the treatment of diabetes is consistent with the present specification. The examiner uses the present specification as a definition of the term "patient in need of" the claimed treatments.

Secondly, Howard teaches that:

> dyslipidemia contributes to the atherosclerotic process in diabetic individual (paragraph at top of page 216);
>
> the leading cause of death for individuals with diabetes is cardiovascular disease, and one of the most important factors that contribute to this is the alteration in lipoproteins that occur in diabetic subjects (page 216, left column, "Introduction");
>
> Agents which improve glycemic control sometimes also result in improvements in diabetic dyslipidemia (page 218, right column, full paragraph 1).
>
> the cornerstone of therapy for diabetic patients should essentially consider the management of dyslipidemia along with the hyperglycemia, hypertension, and obesity (page 219, left column).

The examiner uses Howard to show that a diabetic patient is a "patient in need of" the claimed treatments because the treatment of diabetes overlaps the treatment of dyslipidemia, cardiovascular disease, hypertension, and obesity.

Thirdly, diabetic patients can also be obese patients, as evidenced by Efendic (paragraph bridging columns 5-6). Thus, an obese, diabetic patient is a "patient in need of" the claimed treatments because the treatment of obesity overlaps the treatment of diabetes.

Fourthly, one of ordinary skill in the art would administer the GLP-1 agonist for the treatment of diabetes or obesity, as taught in the claims of the patents, with the intention of the intention of improving glycemic control and improving diabetic dyslipidemia because the cornerstone of therapy for diabetic patients should essentially consider the management of dyslipidemia along with the hyperglycemia, hypertension, and obesity and agents which improve glycemic control sometimes also result in improvements in diabetic dyslipidemia.

Appellants argue that just as in Rapoport, the prior art relied upon by the examiner does not disclose administering something to patients with the specific intent of achieving the results in the present claims. Applicant's arguments have been fully considered but they are not persuasive. In Rapoport, both intrinsic evidence and the plain meaning of the term "method for treatment of sleep apneas" supported construction of the term as being limited to treatment of the underlying sleep apnea disorder itself, and not encompassing treatment of anxiety and other secondary symptoms related to sleep apnea. However, the present specification discloses treatment for diseases that may be alleviated by lowering serum lipid levels, including, e.g., cardiovascular disease and diabetes, by administering a GLP-1 agonist. Thus, a "patient in need of" the claimed treatments overlaps the treatment of cardiovascular disease, diabetes, and

obesity, as discussed above. The claims of the cited patents disclose the treatment of diabetes or obesity with Arg^{34},Lys^{26}(N^{M}-K-Glu(N^{I}-hexadecanoyl)))GLP-1(7-37). The present claims are directed to or encompass the administration of Arg^{34},Lys^{26}(N^{M}-K-Glu(N^{I}-hexadecanoyl)))GLP-1(7-37). Furthermore, Arg^{34},Lys^{26}(N^{M}-K-Glu(N^{I}-hexadecanoyl)))GLP-1(7-37) is an analog or derivative or a derivative of an analogue of GLP-1(7-37) or exendin, as recited in the present claims. One of ordinary skill in the art would administer the GLP-1 agonist for the treatment of diabetes or obesity, as taught in the claims of the patents, with the intention of improving glycemic control and improving diabetic dyslipidemia because the cornerstone of therapy for diabetic patients should essentially consider the management of dyslipidemia along with the hyperglycemia, hypertension, and obesity and agents which improve glycemic control sometimes also result in improvements in diabetic dyslipidemia. In other words, the claims of the cited patents encompass achieving the results in the present claims.

(12) Relevant prior art not relied upon by the examiner.

The following prior art is cited for the record:

Juntti-Berggren (The antidiabetogenic effect of GLP-1 is maintained during a 7-day treatment period and improves diabetic dyslipoproteinemia in NIDDM patients. Diabetes Care. 1996 Nov;19(11):1200-6) discloses that dyslipoproteinemia is a common feature of patients with NIDDM and that treatment of the diabetic state leads to improvement of the plasma lipoprotein profile (page 1200, right column, full paragraph 2).

Banchovin (WO 99/38501, cited by Applicants) teaches that hyperlipoproteinemia is a complication of diabetes. The cumulative effect of these diabetes-associated abnormalities is

severe blood vessel and nerve damage. See page 2, full paragraph 1. Banchovin provides improved methods for reducing hyperlipidemia and/or hyperlipoproteinemia and for abating atherosclerosis (page 3, lines 29-31) and methods for producing beneficial changes in blood lipoprotein levels, and thus to provide effective treatments for diabetes, obesity and/or atherosclerosis (page 4, full paragraph 3). The method includes the administration of an inhibitor which inhibits the proteolysis of GLP-1 and accordingly increases the plasma half-life of GLP-1 (page 5, last full paragraph).

Beeley (WO 98/30231, cited by Applicants) discloses the administration of an effective amount of an exendin or an exendin agonist for treating conditions or disorders which can be alleviated by reducing food intake. The methods are useful for treating conditions or disorders, including obesity, Type II diabetes, eating disorders, and insulin-resistance syndrome. The methods are also useful for lowering the plasma glucose level, lowering the plasma lipid level, reducing the cardiac risk, reducing the appetite, and reducing the weight of subjects. See the Abstract.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

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DSR
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